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# Novel Stereocontrolled Addition of Allylmetal Reagents to α-Imino Esters: Efficient Synthesis of Chiral Tetrahydroquinoline Derivatives†

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To prepare in multigram scale new antagonists of the glycine binding site associated to the NMDA receptor, an efficient distereoselective route was set up. The addition of suitable allyltin reagents to chiral *N*-aryl α-imino esters (*R*-(+)-*tert*-butyl lactate used as chiral auxiliary), gave the corresponding α amino acid-type derivative in high chemical yield and optical purity. This allylation reaction represents a novel example of efficient long-range stereodifferentiation process. In the last part of the synthesis, a regioselective Heck-type cyclization reaction enabled preparation of the target tetrasubstituted exocycle and trisubtituted endocycle double bond derivatives.

## Introduction

The modulation of the NMDA receptor[1] by antagonists acting at the glycine binding site is perceived as one of the most promising biological strategies to identify effective antihyperalgesic agents able to manage chronic pain,[2] an area still associated with high unmet needs in current medicine. This pathophysiological event occurs when tissues and/or nerves are damaged (e.g. neoplastic infiltration, inflammation, ischaemia), resulting in the alteration of the physiological relationship existing between painful stimuli and somatosensory response.[3] A significant body of evidence supports the hypothesis that the activation of the ion-channel associated with the NMDA receptor is responsible for the abnormal entry of $Ca^{2+}$ to the postsynaptic neurones, massive depolarization[4] and increased excitability of spinal cord neurons, a phenomenon known as *wind-up*. This biochemical event is associated with the onset of severe and prolonged pain states (hyperalgesia/allodynia). Glycine antagonists, blocking the overactivation of the NMDA receptor and restoring the baseline level of nociceptive transmission, should be effective for the treatment of the chronic pain.[5]

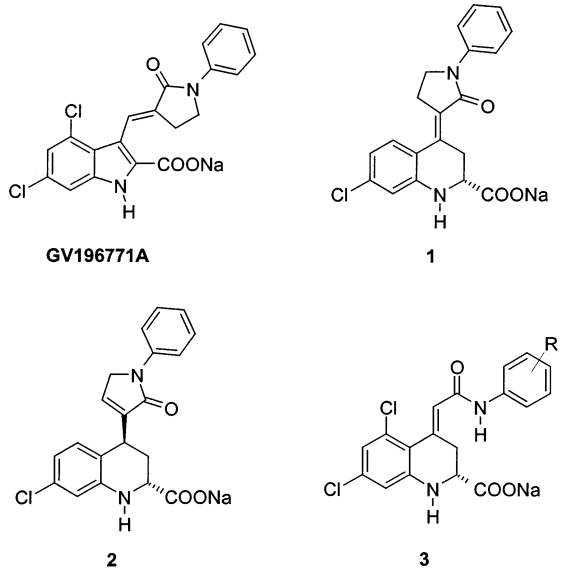


**FIGURE 1.** Indole 2-carboxylates and THQ derivatives as glycine antagonists.

The extensive exploration performed by our group in this field allowed the identification of the indole-2-carboxylate derivative GV196771A,[6] shown in Figure 1. Remarkably, in animal models of chronic pain this compound was found to be highly effective in conditions distinct from those of classical opioids.

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† Dedicated to the memory of John A.Winders.

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(1) *The NMDA Receptor*, 2nd ed.; Collingridge, G. L., Watkins, J. C., Eds.; IRL Press: Oxford, England, 1994.

(2) (a) Woolf, C. J. *Nature* **1983**, *306*, 686. (b) Davies, S. N.; Lodge, D. *Brain Res.* **1987**, *424*, 402. (c) Haley, J. E.; Sullivan, A. F.; Dickenson, A. H. *Brain Res.* **1990**, *518*, 218. (d) Woolf, C. J.; Thompson, S. W. N. *Pain* **1991**, *44*, 299. (e) Woolf, C. J. *Pulm. Pharmacol.* **1995**, *8*, 161. (f) Harris, J. A.; Corsi, M.; Quartaroli, M.; Arban, R.; Bentivoglio, M. *Neuroscience* **1996**, *74*, 7. (g) Dickenson, A. H.; Chapman, V.; Green, G. M. *Gen. Pharmacol.* **1997**, *28*, 633.

(3) Jessel, T. M.; Kelly, D. D. Pain and Analgesia. In *Principles of Neural Science*; Kandel, E. R., Schwartz, J. H., Jessell, T. H., Eds.; Appleton & Lange: 1991; pp 385−399.

(4) Dickenson, A. H.; Chapman, V.; Green, G. M. *Gen. Pharmacol.* **1997**, *28*, 633.

(5) For a review on the drugs currently used to treat chronic pain see: Karlsten, R.; Gordh, T. *Drugs Aging* **1997**, *11*, 398.

(6) (a) Di Fabio, R.; Conti, N.; Corsi, M.; Donati, D.; Gastaldi, P.; Gaviraghi, G.; Giacobbe, S.; Pentassuglia, G.; Quartaroli, M.; Ratti, E.; Trist, D. G.; Ugolini, A. *Drugs Fut.* **2000**, *25*, 137. (b) Quartaroli, M.; Carignani, C.; Dal Forno, G.; Mugnaini, M.; Ugolini, A.; Arban, R.; Bettelini, L.; Maraia, G.; Belardetti, F.; Reggiani, A.; Trist, D. G.; Ratti, E.; Di Fabio, R.; Corsi, M. *J. Pharmacol. Exp. Ther.* **1999**, *1*, 290. (c) Giacobbe, S. A.; Baraldi, D.; Di Fabio, R. *Biorg. Med. Chem. Lett.* **1998**, *8*, 1689.

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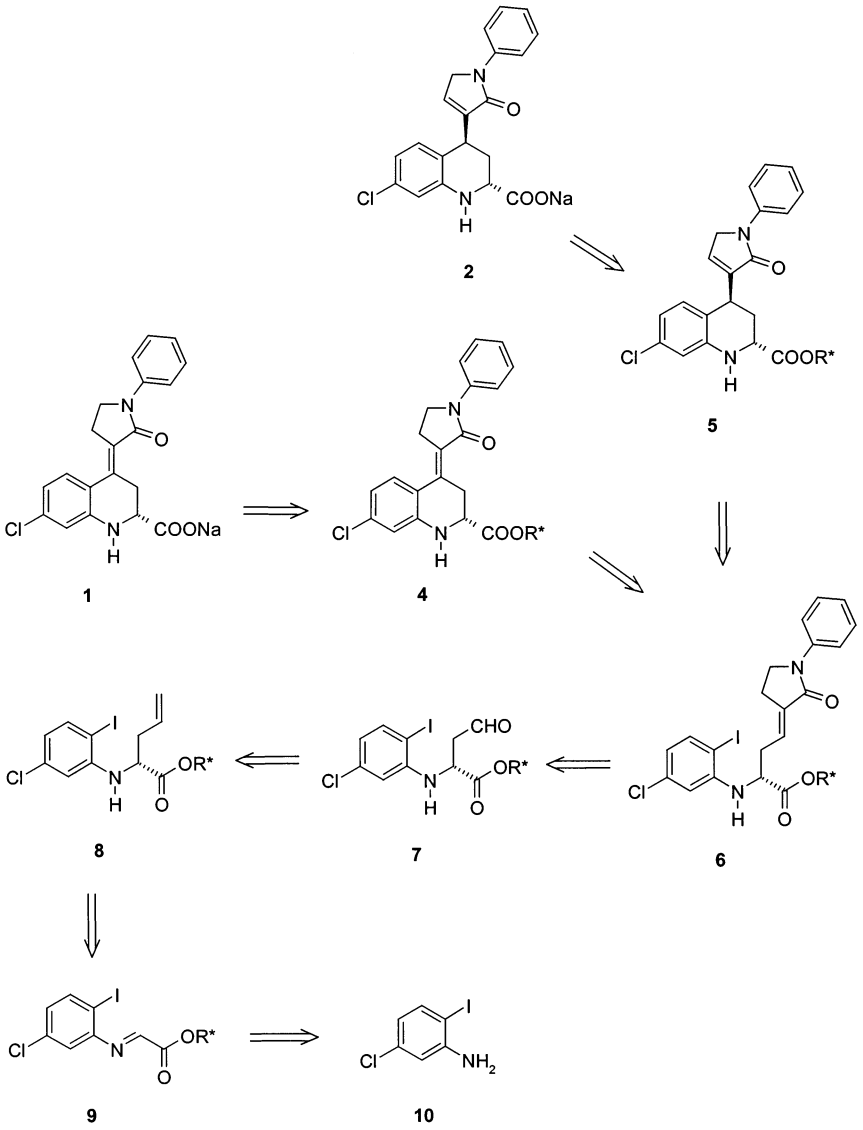
**SCHEME 1. Retrosynthetic Approach to the THQ Scaffold**




Tetrahydroquinoline (THQ) derivatives **1** and **2**, shown in Figure 1, were identified during the drug discovery program, as potential alternatives to GV196771A. To prepare these compounds in multigram scale, an efficient synthesis was set up in which the key steps are represented by (a) the stereocontrolled formation of the C-2 α amino acid-type stereogenic center; (b) the Heck-type cyclization reaction to give selectively the *exo* or the *endo* derivatives of type **1** and **2**. To that end, the addition of allyltin derivatives to suitable *N*-aryl α-imino esters, in which commercially available *R*-(+)-*tert*-butyl lactate was used as chiral auxiliary, and the use of specific Heck-type reaction conditions, respectively, enabled us to overcome these synthetic issues. In particular, as far as the allylation reaction is concerned, the presence of lactate esters was crucial to achieve high diastereocontrol, opening novel perspectives in stereoselective addition reactions to α-iminoesters for the preparation of both natural and unnatural amino acids.

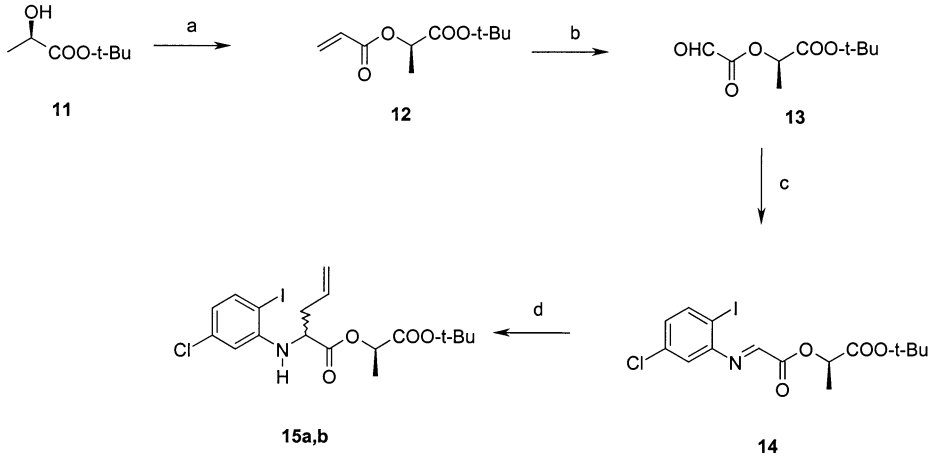
## Results and Discussion

The retrosynthetic analysis, proposed for the synthesis of tetrahydroquinoline derivatives **1** and **2**, is shown in Scheme 1. Considering the possibility of performing a Wittig-type olefination reaction to introduce the α,*β*-unsaturated *N*-phenyl *γ*-lactam moiety, followed by a Heck-type cyclization,[7] the sequential dissection of the $C_{4-5}$ *exendo* bond of compounds **1** and **2** and the double bond of intermediate **6**, respectively, seemed to be the most appropriate strategy to attempt. Therefore, the identification of an efficient synthetic procedure to prepare in large scale the enantiomerically pure *N*-aryl allylglycine derivative **8**, was perceived as the most urgent problem to solve. Among the different potential approaches, it was speculated that the addition of an allylmetal derivative, in the presence of a suitable Lewis acid, to a chiral *N*-aryl aldimine of type **9**, could afford compound **8**, as a mixture of diastereoisomers, hopefully separable by chromatography.[8] The degree of *π*-facial diastereocontrol of the allylation reaction could depend

(7) (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons Ltd: Chichester, 1995. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.

(8) For the synthesis of a different series of racemic THQ analogues identified within the glycine antagonists-stroke program, see: Di Fabio, R.; Alvaro, G.; Bertani, B.; Giacobbe, S. *Can. J. Chem.* **2000**, *6*, 78.

**SCHEME 2. Allylmetalation Reaction**[a]




[a] (a) Acryloyl chloride, DMAP, $CH_2Cl_2$, 0 °C then rt, 2 h, 88%; (b) $OsO_4$, $NaIO_4$, THF/$H_2O$, 3:1, rt, 12 h, 100%; (c) i. toluene, reflux; ii. 5-chloro-2-iodoaniline, 100%; (d) $TiCl_4$, $CH_2Cl_2$, −78 °C, 15 min then allyltributyltin −78 °C, 1 h, 90%.

on the nature of both the chiral auxiliary R* selected and the kind of metal used.[9] A key requirement in the choice of R* was the need to deprotect that group under mild reaction conditions, to avoid the potential racemization of the α amino acid-type stereogenic center.[10]

From the synthesis of the tetrahydroquinoline derivatives of type **3**, shown in Figure 1, it was known that the corresponding *R*-(+)-*tert*-butyl lactate ester derivative (prepared from the corresponding racemic carboxylic acid derivative by Mitsunobu reaction[11] followed by chromatographic separation of the diasteroisomers) could be hydrolyzed, with LiOH in EtOH/$H_2O$ at room temperature for 1 h, to afford the pure enantiomer without epimerization of the *N*-aryl α-amino acid stereogenic center. On the basis of this observation, an attempt to use *R*-(+)-*tert*-butyl lactate as chiral auxiliary in the allylmetalation reaction was performed as shown in Scheme 2. To prepare the chiral aldimine **14**, the commercially available *R*-(+)-*tert*-butyl lactate **11** was reacted with acryloyl choride in $CH_2Cl_2$ at 0 °C in the presence of a catalytic amount of DMAP, to give the intermediate **12** in high yield. The following oxidative cleavage of the double bond, with $OsO_4$ and $NaIO_4$, furnished the glyoxylate ester **13**. This intermediate was reacted overnight with 5-chloro-2-iodoaniline in refluxing toluene, with azeotropic removal of water using a Dean−Stark apparatus and in the presence of anhydrous $MgSO_4$, to furnish the desired aldimine derivative **14** in quantitative yield, as a stable compound. When **14** was dissolved in dry $CH_2Cl_2$ and reacted at −78 °C with an excess of $TiCl_4$ (1.1 equiv) and allyltributyltin (1.5 equiv), an inseparable mixture by flash chromatography of diastereoisomers **15a** and **15b** (ratio 80:20 by HPLC analysis) was isolated in 90% total yield. Remarkably, despite the unfavorable $C_{1-4}$ relationship existing between the lactate stereogenic center and the aldimine reaction center, a promising level of $\pi$-facial diastereoselection was observed.

To investigate further the stereoelectronic features of the lactate ester responsible for the significant degree of stereocontrol observed, an attempt was made to assign the absolute configuration of the stereogenic center of the major diastereoisomer. To that end, as shown in Scheme 3, the *p*-methoxyphenyl aldimine derivative **16**, smoothly prepared as described for the analogous intermediate **14**, was transformed into the methyl ester of *R*-(−)-norvaline. This sequence is feasible due the possibility of deprotecting the *p*-methoxyaryl moiety at the end of the synthetic sequence to restore[12] the desired α-amino acid derivative. As expected, when reactive intermediate **16** was treated with allyltributyltin and $TiCl_4$ at −78 °C in $CH_2Cl_2$, diastereoisomers **17a** and **17b** were isolated in the same 80:20 ratio previously observed from the allylation reaction with the aldimine **14**. The most abundant compound **17a**, after purification by flash chromatography, was transformed into the corresponding carboxy derivative **19** by sequential hydrogenation with Pd/C 10% in EtOH at 4 atm followed by hydrolysis of the *R*-(+)-*tert*-butyl lactate with LiOH in a 2:1 mixture of THF/$H_2O$. This intermediate was then reacted with $TMSCHN_2$ to give the corresponding methyl ester **20**. The *p*-methoxy phenyl group was removed by cerium ammonium nitrate in $CH_3CN-H_2O$ 10:1 at −25 °C, to give the desired *R*-(−)-norvaline methyl ester **21** in moderate yield, after purification by flash chromatography. This compound was found to be identical both in terms of chiral HPLC and CZE analysis to authentic *R*-(−)-norvaline methyl ester, readily prepared from the commercially available amino acid. Therefore, from this correlation study it was possible to conclude that the *R*-(+)-lactate ester was able to induce, in the allylation reaction, the preferential formation of a (*R*) stereogenic center.[13]

With the aim of optimizing further the diastereoselectivity observed, this allylmetalation reaction was re-

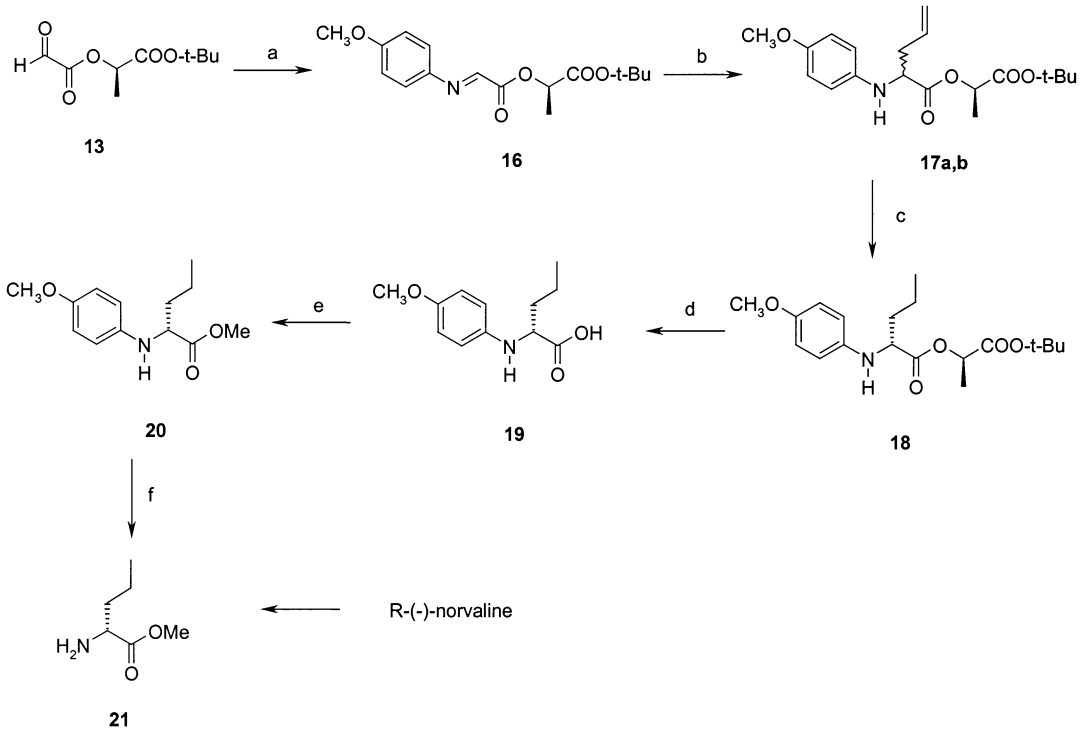
(9) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(10) For a relevant example of the diastereoselective addition of organometallic compounds to chiral α-imino esters, see: Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5423. The use of the cited 8-(−)-phenylmenthyl ester, as chiral auxiliary, was unsuccessful in our case, due to the insurmountable difficulty to remove it at the end of the synthesis, avoiding racemization of the C-2 stereogenic center in basic medium (LiOH), or the extensive degradation of the THQ scaffold in the presence of $BCl_3$.

(11) For two reviews on the Mitsunobu reaction, see: (a) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127−164. (b) Dodge, J. A.; Jones, S. A. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 273−283.

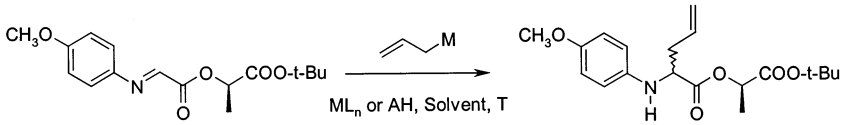
(12) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474.

**SCHEME 3. Determination of the Absolute Stereochemistry**[a]




[a] (a) 4-Methoxyaniline, toluene, reflux, 30 min; (b) $TiCl_4$, $CH_2Cl_2$, −78 °C, 20 min, then allyltributyltin, 30 min, 80%; (c) Pd/C 10%, EtOH, $H_2$ (4 atm), 6 h, 96%; (d) LiOH, THF/$H_2O$ 2:1, rt, 66%; (e) trimethylsilyldiazomethane, rt, $CH_2Cl_2$/MeOH 1:1, 90%; (f) CAN, $CH_3CN$/$H_2O$ 8:1, −25 °C, 40 min, 45%.

**TABLE 1. Allylmetalation Reaction: Intermolecular Addition**

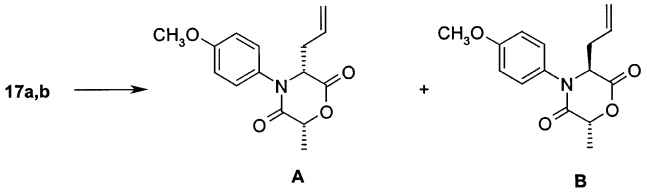



| entry | ML$_n$ or AH | M | solvent | T | ratio[a] **17a**/**17b** |
|---|---|---|---|---|---|
| 1 | − | $SnBu_3$ | $CH_2Cl_2$ | −78 °C | − |
| 2 | $TiCl_4$ | $SnBu_3$ | $CH_2Cl_2$ | −78 °C | 80:20 |
| 3 | $ZnI_2$ | $SnBu_3$ | $CH_2Cl_2$ | −78 °C | 70:30 |
| 4 | $Sc(OTf)_3$ | $SnBu_3$ | $CH_2Cl_2$ | −78 °C | 71:29 |
| 5 | $Yb(OTf)_3$ | $SnBu_3$ | $CH_2Cl_2$ | −78 °C | 68:32 |
| 6 | $BF_3{\cdot}Et_2O$ | $SnBu_3$ | $CH_2Cl_2$ | −78 °C | 72:28 |
| 7 | p-TsOH | $SnBu_3$ | $CH_2Cl_2$ | −78 °C | 75:25 |

[a] Determined by HPLC.

peated on the aldimine **16** with different Lewis and Bröensted acids. As shown in Table 1, a similar degree of diastereoselectivity was obtained independently of the nature of the Lewis or Bröensted acid used. In particular, when *p*-TsOH or $BF_3{\cdot}Et_2O$ (entries 7 and 6, respectively) were used, the degree of diastereoselectivity did not change significantly with respect to the reactions performed in the presence of $TiCl_4$, $ZnI_2$, $Sc(OTf)_3$, and $Yb(OTf)_3$, (entries 2, 3, 4, and 5, respectively). On the basis of these results, it was speculated that (a) the coordination or the protonation of the nitrogen of the α-iminoester by the Lewis or Bröensted acid is crucial to promote the allylation reaction; (b) the presence of (*R*)-lactate ester is responsible for the preferential attack of the allyl moiety on Re face of the imine.[14] As shown in Figure 2, the level of induction observed can be accounted for by an "open-chain" or "chelated" imine complex (in the latter

(13) This result was confirmed by NOE studies performed on the cyclic diastereoisomers **A** and **B**. These compounds were smoothly prepared from the 80:20 mixture of **17a** and **17b** by sequential chemoselective hydrolysis of the *tert*-butyl ester group followed by cyclization with EDC and HOBT in DMF at room temperature, and finally separation by flash chromatography.



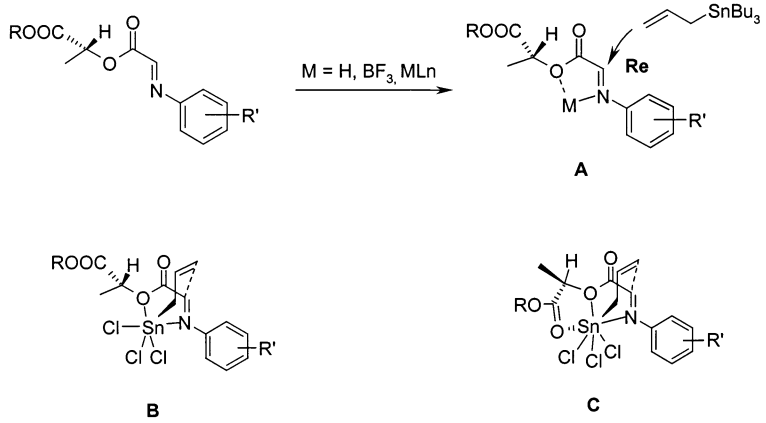



**FIGURE 2.** Allylmetalation reaction: proposed mechanism.

**TABLE 2. Allylmetalation Reaction: Intramolecular Addition**

| entry | $ML_n$ | M | solvent | T | % conversion[a]/*t* | ratio[a] **17a**/**17b** |
|---|---|---|---|---|---|---|
| 1 | – | MgCl | THF | −78 °C | – | – |
| 2 | $Zn(CH_3)_2$ | MgCl | THF | −78 °C | 75/1 h | 28:72 |
| 3 | – | ZnBr | THF | −78 °C | 75/1 h | 67:33 |
| 4 | – | $SiCl_3$ | DMF | 0 °C | 50/2 h | 48:52 |
| 5 | – | $SnICl_2$ | THF | 0 °C | 70/2 h | 93:7 |
| 6 | – | $SnICl_2$ | $CH_2Cl_2$ | −78 °C | 20/2 h | >98:2 |
| 7 | – | $SnCl_3$ | $CH_2Cl_2$ | −78 °C | 100/15 min | >98:2 |

[a] Determined by HPLC

case the imine moiety could act both as a bidentate or tridentate ligand), in which the nucleophilic attack occurs preferentially anti to the COOR group of the lactate.[15] According to this transition state model, when α-iminoester **16** was precomplexed with $Zn(CH_3)_2$ and then reacted with allylmagnesium chloride (Table 2, entry 2), an opposite induction was observed (**17a**/**17b**, 28:72).[16] In this case, the Grignard reagent should be, in fact, coordinated by the COOR group of the lactate with preferential delivery of the allyl moiety to the Si face of the imine.

To maximize the degree of diastereoselectivity, further investigations were performed using zinc, silicon, and tin allylmetals, this time without the addition of Lewis acids. The results achieved are summarized in Table 2. The diastereomeric ratio did not vary significantly with respect to the reactions shown in Table 1 in the case of allylzinc bromide (entry 3).[17] When aldimine **16** was treated at 0 °C in DMF with an equimolar amount of allyltrichlorosilane,[18] a slow reaction occurred (50% conversion after 2 h) and the diastereocontrol of the reaction was completely lost (entry 4; **17a**/**17b**, 48:52). Conversely, remarkable results were obtained when aldimine **16** was added, at 0 °C in THF, to a preformed solution of allyliododichlorotin[19] in THF (entry 5), to give diastereoisomers **17a** and **17b** in a 93:7 ratio. The level of stereocontrol achieved was even higher in $CH_2Cl_2$ (entry 6; **17a**/**17b**, >98:2), but the conversion after 2 h at −78 °C was very low. Finally, the best results were achieved with allyltrichlorotin[20] at −78 °C in $CH_2Cl_2$. This reaction was complete after 15 min, affording **17a** as the only diasteroisomer (entry 7; **17a**/**17b**, >98:2), in 77% total yield from **16** after purification by flash chromatography.[21]

On the basis of the degree of diastereoselectivity observed, this allylation reaction can be considered as a novel example of an efficient long-range stereodifferentiation process using, as chiral auxiliary, a cheap molecule belonging to the chiral pool, particularly useful, therefore, for preparative purposes. The stereochemical control achieved could be explained, as shown in Figure 2, in terms of an intramolecular-type addition reaction via formation of a more rigid hexa-coordinated tin transition state complex (B), in which the COOR group of the lactate is coordinated by tin.[22]

The optimized allylation reaction was applied to the synthesis of the target compounds **1** and **2**. As shown in Scheme 4, when allyltrichlorotin was reacted with the aldimine **14**, the desired allyl derivative **15** was obtained, once again, as a single diastereoisomer in 90% yield in two steps from 5-chloro-2-iodoaniline. Remarkably, the

(14) For a similar transition state model proposed for asymmetric Diels−Alder reactions performed on acrylic acid lactate esters, see: (a) Hampley, P.; Helmchen, G.; Holmes, A. B.; Marshall, D. R.; MacKinnon, J. W. M.; Smith, D. F.; Ziller, J. W. *J. Chem. Soc. Chem. Commun.* **1992**, 786. (b) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112.

(15) When the *tert*-butyl ester was replaced by the less sterically demanding methyl ester, in the presence of $TiCl_4$, a slightly reduced stereocontrol was observed (**17a**/**17b**, 70:30 vs 80:20 for the methyl ester and *tert*-butyl ester, respectively). This minimal dependence of the diastereoselectivity on the kind of lactate ester used seems to confirm this hypothesis.

(16) Reaction with the *ate*-complex allyl$(ZnCH_3)_2MgCl$ in $CH_2Cl_2$ at −78 °C furnished a complex mixture of reaction products.

(17) (a) Fishwick, M. F.; Wallbridge, M. G. H. *J. Organomet. Chem.* **1977**, *136*, C46−C48. (b) Alvaro, G.; Savoia, D. *Tetrahedron Asymmetry* **1996**, *7*, 2083.

(18) For the addition of allyltrichlorosilane to benzoylhydrazones, see: Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942.

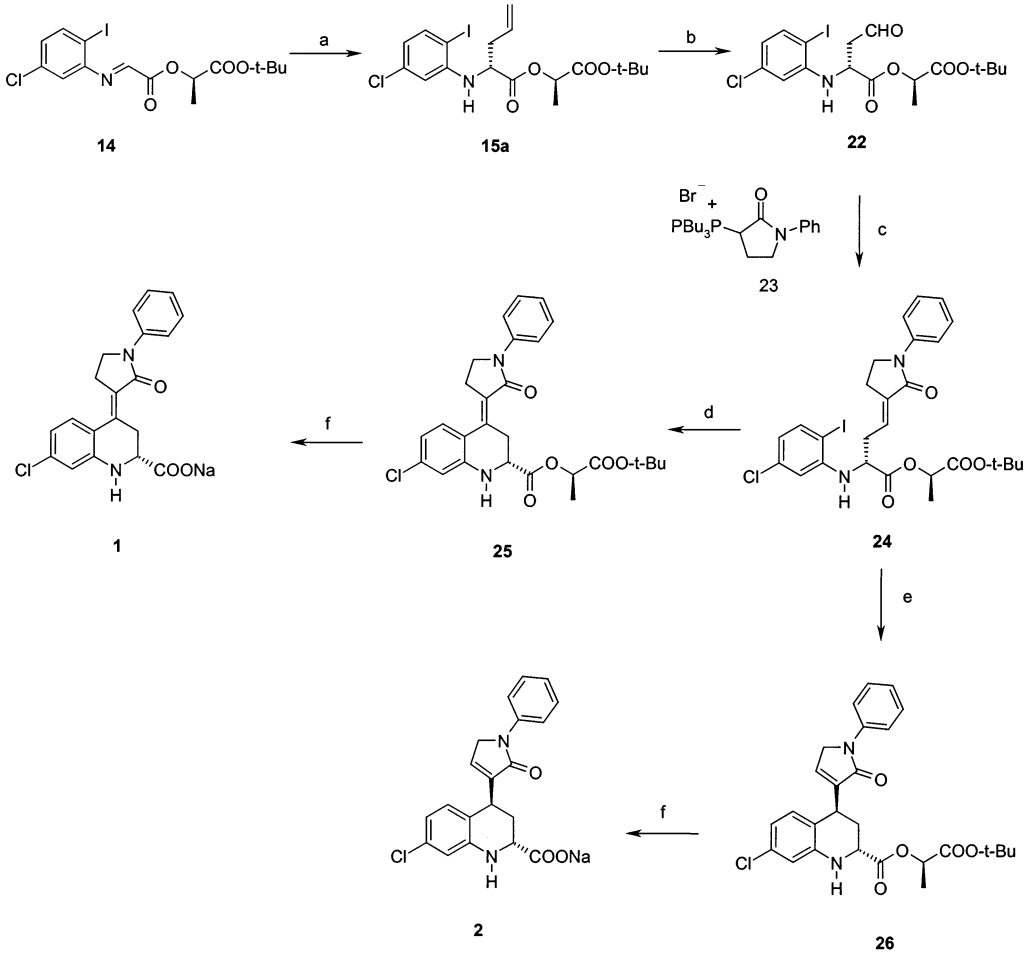
(19) (a) Alvaro, G.; Boga, C.; Savoia, D.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, *9*, 875. (b) Alvaro, G.; Savoia, D. *Tetrahedron Asymmetry* **1996**, *7*, 2083.

(20) Fishwich, M. F.; Wallbridge, M. G. H. *J. Orgamet. Chem.* **1977**, *136*, C46−C48.

(21) For the addition reaction of substituted chiral allyltrichlorotin derivatives to α-iminoesters see: Hallett, D. J.; Thomas, E. J. *Tetrahedron Asymmetry* **1995**, *6*, 2575.

(22) At this moment in time the formation of a heptacoordinated complex (imine as a tridentate ligand) or, as widely reported for silicon, the formation of a hexacoordinated cationic complex, resulting from dissociation of a single chlorine ion cannot be excluded. For some examples of silicon complexes dealing with the latter hypothesis, see: (a) Denmark, S. E.; Stavenger, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 8837. (b) Denmark, S. E.; Stavenger, R. A.; Wong, K. T.; Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982 and references therein. (c) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351.

**SCHEME 4. Diastereoselective Synthesis of Compounds 1 and 2**[a]




[a] (a) i. Allyltributyltin, $CH_2Cl_2$, $SnCl_4$, −78 °C, 20 min, 90%; ii. 14, −78 °C, 20 min, 77%; (b) $O_3$, $CH_2Cl_2$, −78 °C then $PPh_3$, 2 h, 55%; (c) tributyl-3-(1-phenylpiperidone) phosphonium bromide, DBU, $CH_3CN$, −20 °C, 3 h, 70%; (d) $Pd(PPh_3)_4$, triethylamine, toluene, reflux, 3.5 h, 85%; (e) $Pd(OAc)_2$, triethylamine, DMF, 120 °C, 3 h, 70%; (f) LiOH, $THF/H_2O$ 3:1, 1 h, rt, 85−90%.

same results were obtained when the reaction was repeated on multigram scale, confirming both the degree of diasteroselectivity achieved and the robustness of the method. Having solved this key issue, the following aldehyde derivative **22**, prepared in good yield by ozonolysis at −78 °C in $CH_2Cl_2$, was efficiently transformed into the α,β-unsaturated γ-lactam intermediate **24** by Wittig-type olefination reaction with tributyl-3-(1-phenylpiperidone) phosphonium bromide[6a] **23** in $CH_3CN$ at room temperature in the presence of a stoichiometric amount of DBU. Good stereochemical control of the double bond was observed (ratio $E/Z$ = 85:15) and the desired *E* isomer was isolated in 70% yield by flash chromatography. As expected, when **24** was submitted to the following Heck-type ring closure reaction[23] in DMF in the presence of a catalytic amount of $Pd(PPh_3)_4$ and 2 equiv of TEA at 120 °C for 1 h, a mixture of the *exo* double bond derivative **25** and the corresponding *endo* compound **26**, readily separable by flash chromatography, was obtained in 80% total yield (ratio 60:40).[24] As far as compound **26** is concerned, it is worth underlining that the stereochemistry of the new C-4 stereogenic center was completely controlled with the formation of the C-2/C-4 anti compound only. Finally, as expected, the hydrolysis of the lactate ester gave the enantiomerically pure compounds **1** and **2**, without any detectable racemization. As shown in Supporting Information, the 50% thermal ellipsoid plot from the X-ray analysis of compound **1**, as its meglumine salt, confirmed the (*R*) absolute configuration of the C-2 stereogenic center.[25]

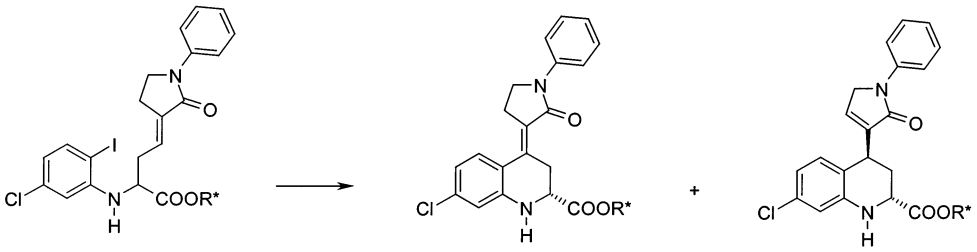
To increase the efficiency of the synthetic route, this Heck-type cyclization reaction was studied in more detail with the aim of identifying reaction conditions to obtain selectively either compound **25** or **26**. The results obtained are shown in Table 3. In this event, the Pd catalyst, along with the solvent and reaction conditions, were varied. First of all, no significant changes of the ratio **25**:**26** was observed when the reaction was run for

(23) For reviews on the Heck reaction, see: (a) Gibson, S. E.; Middleton, R. J.; *Contemp. Org. Synth.* **1996**, *3*, 447. (b) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (c) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *36*, 2379. (d) Heck, R. F. *Org. React.* **1982**, *27*, 345.

(24) For a related example of an intramolecular cis addition/syn elimination reaction, see: (a) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523. (b) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedon Lett.* **1991**, *32*, 4937.

(25) It should be noted that the numbering scheme of **1** in Supporting Information is arbitrary, and that C-9 in the diagram corresponds to C-2.

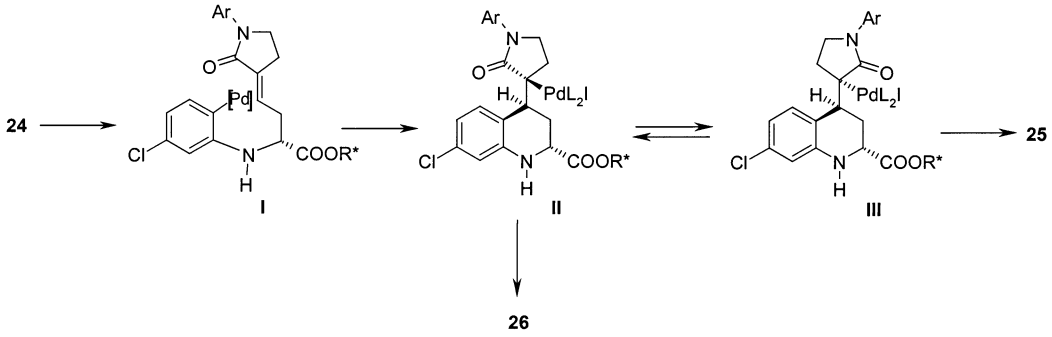
**TABLE 3. Heck Cyclization Reaction: Endo/Exo Selectivity**



**24** **25** **26**

| entry | catalyst | solvent | *T*/*t* | **25**:**26** (yield) |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$, TEA (2 equiv) | DMF | 120 °C/1 h | 60:40 (80%) |
| 2 | $Pd(PPh_3)_4$, TEA (2 equiv) | DMF | 120 °C/8 h | 60:40 (80%) |
| 3 | $Pd(OAc)_2$, $PPh_3$, TEA (1 equiv) | $CH_3CN$ | 100 °C/6 h | 55:45 (75%) |
| 4 | $Pd(OAc)_2$, TEA (1 equiv) | DMF | 110 °C/1 h | 0:100 (70%) |
| 5 | $Pd(OAc)_2$, tri-*o*-tolylphosphine, TEA (1.5 equiv) | DMF | 120 °C/3 h | 0:100 (42%) |
| 6 | $Pd(OAc)_2$, $PPh_3$, $Ag_2CO_3$ (1.5 equiv) | DMF | 120 °C/1 h | 0:100 (63%) |
| 7 | $Pd(PPh_3)_4$, TEA (2 equiv) | toluene | 100 °C/3.5 h | 96:4 (90%) |

**SCHEME 5. Heck Cyclization Reaction: Proposed Mechanisms**



longer times, up to 8h (entry 2). Using $Pd(OAc)_2$, $PPh_3$, and TEA in $CH_3CN$ at reflux a similar result in terms of ratio the **25**:**26** was observed (entry 3), whereas, when the reaction was performed with $Pd(OAc)_2$ without the addition of $PPh_3$, compound **26** was isolated as the only reaction product (entry 4). The same degree of regioselectivity was observed with $Pd(OAc)_2$ in the presence of tri-2-*o*-tolylphosphine,[26] or with $PPh_3$ in the presence of $Ag_2CO_3$ (entries 5 and 6, respectively).[27] The complete regiocontrol observed in the formation of the double bond, could be explained based on the greater tendency of the intermediate Pd-complex **II** (Scheme 5) to dissociate neutral ligands (such as DMF or tri-o-tolylphosphine[26a]) or iodide in the presence of $Ag_2CO_3$,[27b] to give compound **26** exclusively.

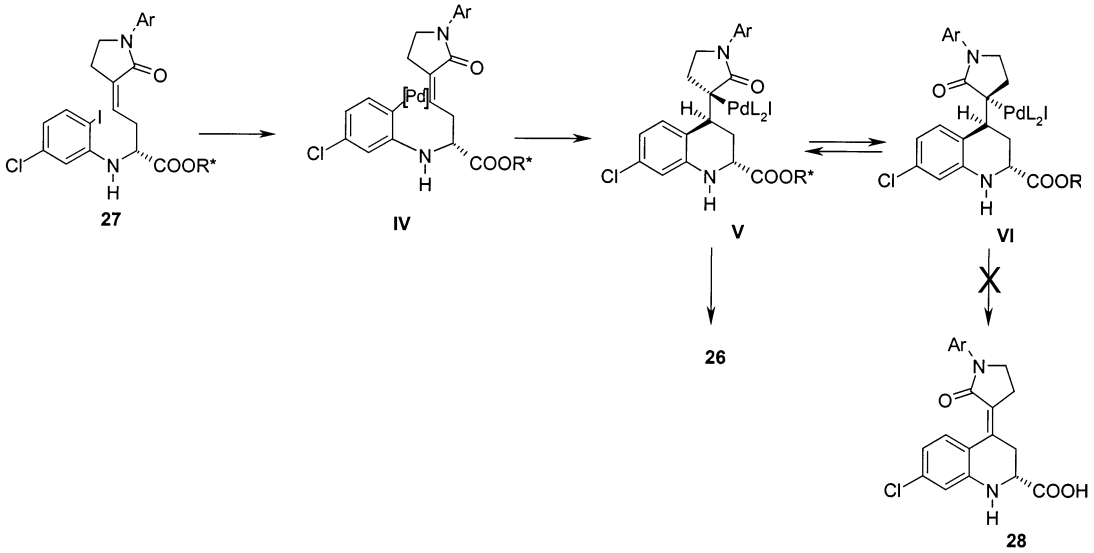
Remarkably, when the reaction was carried out with $Pd(PPh_3)_4$ and TEA in toluene at 100 °C for 2 h, the selectivity of the cyclization was completely reversed (entry 7), and compound **25** and **26** were obtained in a 96:4 ratio in 90% total yield. In this case, the increased stability of the intermediate Pd-complex **II** in a poor dissociating solvent (toluene) is probably responsible for the evolution of the system toward the preferential formation, through the rotamer **III**, of the most thermodynamically stable compound **25**. Finally, as shown in Scheme 6, when the *Z*-type olefin derivative **27** was reacted with $Pd(PPh_3)_4$ and TEA, the derivative **26** was obtained as the only reaction product, probably due to the unfavored transformation, for steric reasons, of the intermediate **V** into its rotational isomer **VI**. Based on this result, to prepare compound **26** it was not necessary to separate **24** from **27** and indeed, when the mixture of the *E* and *Z* olefin derivatives (85:15) was reacted as above, compound **26** was isolated in 85% yield after purification by flash chromatography.

In conclusion, an efficient stereoselective synthesis of novel THQ derivatives has been described. In particular, the stereoselective formation of the C-2 α amino acid-type stereogenic center was achieved using lactate as a commercially available, low-cost chiral auxiliary, that can be smoothly deprotected at the end of the synthetic sequence. The stereoelectronic effect played by the ester group of lactate, was hypothesized to be crucial to suitably control the trajectory of approach of the nucleophile to the *N*-aryl aldimine. At the same time, a high degree of regioselectivity was achieved in the Heck-type cyclization reaction. Following this route the *exo* and *endo* compounds **1** and **2** were efficiently obtained on multigram scale.

(26) (a) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C. P.; Riermeier, T. H.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844. (b) Mitsudo, T.; Fischetti, W.; Heck, R. F. *J. Org. Chem.* **1984**, *49*, 1640. (c) Ziegler, C. B.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941.

(27) (a) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603. (b) Abelman, M. W.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4133.

**SCHEME 6. Heck Cyclization Reaction: Proposed Mechanisms**




## Experimental Section

All the reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl; dichloromethane was distilled from $P_2O_5$; anhydrous DMF and $CH_3CN$ were from commercial suppliers and used without further purification. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates (0.25 mm); all $R_f$ values are determined visualizing all spots with UV light (254 nm) and/or phosphomolybdic acid solution. Flash chromatography was performed on silica gel 60 (230−400 mesh). $^1$H and $^{13}$C NMR spectra (400 MHz and 500 MHz) were recorded at 25 °C and $J$ values are given in hertz. In the $^1$H NMR spectra, chemical shifts are reported in ppm to the residual solvent line downfield from the TMS line (as external reference) while in the carbon NMR spectra, the center line $^{13}$C resonance of DMSO-$d_6$ was used as internal reference. NMR assignments are assisted by NOE and 2D-techniques. IR spectra were recorded in $CDCl_3$ solution unless otherwise indicated and are reported in wavenumbers (cm$^{-1}$). Mass spectra were recorded in FAB mode, unless otherwise stated. Melting points (mp) are uncorrected. All optical rotation $[\alpha]_D$ values were obtained in solution, at the sodium D line, at 20 °C. Crystal structure analysis data were collected using $\omega$ rotation with narrow frames.

**(1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl Acrylate (12).** A solution of acryloyl chloride (3.1 mL, 37.4 mmol) in dichloromethane (50 mL) was added dropwise, at 0 °C under a nitrogen atmosphere, to a mixture of (*R*)-*tert*-butyl lactate **11** (2.5 g, 17 mmol), triethylamine (5.4 mL, 37.4 mmol) and 4-(dimethylamino)pyridine (0.415 g, 3.4 mmol) in dry dichloromethane (100 mL). The resulting solution was stirred for 1h at 0 °C and then at room temperature for 2 h. At the end of the reaction 1 M hydrochloric acid (300 mL) was added followed by ethyl acetate (400 mL). The organic layer was separated and washed with brine (300 mL) and then dried over $Na_2SO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 85:15) to give the title compound **12** (3.0 g, 88%) as a colorless oil. IR (film): 1746, 1731 cm$^{-1}$; $^1$H NMR (DMSO) $\delta$ 6.36 (dd, $J$ = 16.8 Hz, 1.5 Hz, 1H), 6.22 (dd, $J$ = 10.5 Hz, 16.8 Hz, 1H), 5.99 (dd, $J$ = 10.5 Hz, 1.5 Hz, 1H), 4.89 (q, $J$ = 6.80 Hz, 1H), 1.40 (d, $J$ = 6.80 Hz, 3H), 1.39 (s, 9H). MS: $m/z$ = 200 [M + H]$^+$. $[\alpha]^{20}_D$ 41.2 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found C, 59.80; H, 8.00.

***tert*-Butyl-(2*R*)-2-[(oxoacetyl)oxy]propanoate (13).** A mixture of intermediate **12** (2.94 g, 15 mmol) in tetrahydrofuran (60 mL) and water (20 mL) was reacted overnight at room temperature with osmium tetroxide (4wt % in water, 2.6 mL, 0.4 mmol) and sodium periodate (8.0 g, 37 mmol). At the end of the reaction the mixture was extracted with diethyl ether (300 mL). The organic phase was separated, dried over $Na_2SO_4$, concentrated in vacuo, and purified by flash chromatography (cyclohexane/ethyl acetate 6:4) to give a colorless, complex mixture of the different hydrate forms (3.3 g, 100%) which was used as such in the next reaction.

***tert*-Butyl-(2*R*)-2-({(2*E*)-2-[(5-chloro-2-iodophenyl)imino]-ethanoyl}oxy) propanoate (14).** A solution of compound **13** (3.3 g, 15 mmol) in toluene (200 mL) was refluxed for 1 h in the presence of a Dean−Stark apparatus. After cooling to room temperature, 5-chloro-2-iodoaniline (4.3 g, 17 mmol) was added, and the solution was refluxed in the presence of $MgSO_4$ for 2 h. After filtration of the $MgSO_4$, the solvent was concentrated in vacuo affording the title compound (6.6 g, 15 mmol, 100%) as a colorless oil, which was used without purification in the next reaction.

**(1*R*) and (1S)-2-(*tert*-Butoxy)-1-methyl-2-oxoethyl-2-(5-chloro-2-iodoanilino)-4-pentenoate (15a,b).** A solution of intermediate **14** (1 g, 2.22 mmol) in dry dichloromethane (30 mL) was cooled to −78 °C, and $TiCl_4$ (1 M in toluene, 2.44 mL, 2.44 mmol) was added dropwise. After 15 min, allyltributyltin (1.1 g, 3.33 mmol) was added, and the resulting suspension was stirred for 1 h. At the end of the reaction, a saturated solution of $NH_4Cl$ (100 mL) was added, and the resulting mixture was extracted with ethyl acetate (2 × 200 mL). The organic layer were collected then washed with brine and dried over $Na_2SO_4$. After filtration, the solvent was concentrated in vacuo and the crude residue purified by flash chromatography (cyclohexane/ethyl acetate 95/5) to afford a 80:20 mixture of diasteroisomers **15a** and **15b** by HPLC analysis, as a colorless oil (0.9 g, 90%).

**(1*R*)-2-(*tert*-Butyl)- 1-methyl-2-oxoethyl-(2*S*)-2-(5-chloro-2-iodoanilino)-4-pentenoate (15a).** To allyltributyltin (2.7 g, 8.18 mmol) dissolved in dichloromethane (100 mL) was added, dropwise at −78 °C, $SnCl_4$ (1 M solution in toluene, 8.2 mL, 8.2 mmol). The solution was stirred for 20 min, and then intermediate **14** (2.39 g, 5.46 mmol) dissolved in dry dichloromethane (50 mL) was added. The reaction was stirred at −78 °C for 15 min, and then a saturated solution of $NH_4Cl$ (100 mL) was added and the resulting mixture was extracted with ethyl acetate (2 × 200 mL). The organic layers were collected and washed with a 10% solution of KF in water. The

organic phase was diluted with diethyl ether (200 mL), filtered, dried over $Na_2SO_4$, and evaporated in vacuo. Final purification of the crude residue by flash chromatography (cyclohexane/ethyl acetate 95:5) gave the title compound **15a** as colorless oil (2.02 g, 77%). $[\alpha]^{20}_D$ 78 (*c* 0.077, $CHCl_3$) IR ($CDCl_3$): 3376, 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.55 (d, $J$ = 8.5 Hz, 1H), 6.47 (dd, $J$ = 8.5 Hz, 2.5 Hz, 1H), 6.43 (d, $J$ = 2.5 Hz, 1H), 5.88 (m, 1H), 5.27 (m, 2H), 5.05 (q, $J$ = 6.82 Hz, 1H), 4.78 (bd, $J$ = 6.5 Hz, 1H), 4.18 (m, 1H), 2.74 (m, 2H), 1.52 (d, $J$ = 6.82 Hz, 3H), 1.47 (s, 9H**)**. Anal. Calcd for $C_{18}H_{23}ClINO_4$: C, 45.07; H, 4.83; N, 2.92. Found C, 45.15; H, 4.85; N, 2.95.

**(1*R*)-2-*tert*-Butyl-1-methyl-2-oxoethyl-(2*S*)-2-(5-chloro-2-iodoanilino)-4-oxobutanoate (22).** Intermediate **15a** (2 g, 4.2 mmol) was dissolved in dichloromethane (200 mL); at −78 °C ozone was bubbled through the solution until the color turned red. Triphenylphosphine (4.4 g, 16.8 mmol) was then added, and the reaction mixture was stirred for 2 h. After evaporation of the solvent in vacuo, the crude mixture was purified by column chromatography (cyclohexane/ethyl acetate 85/15) to afford the title compound **22** (1.1 g, 55%). $[\alpha]^{20}_D$ 26.1 (*c* 0.65, $CHCl_3$) IR ($CDCl_3$): 1739 (C=O); $^1H$ NMR ($CDCl_3$) $\delta$ 9.85 (m, 1H), 7.57 (d, $J$ = 9.5 Hz, 1H), 6.58 (d, $J$ = 2.5 Hz, 1H), 6.51 (dd, $J$ = 9.5 Hz, 2.5 Hz, 1H), 5.04 (q, $J$ = 6.82 Hz, 1H), 4.96 (bd, $J$ = 8.4 Hz, 1H), 4.62 (m, 1H), 3.20 (m, 1H), 3.06 (m, 1H), 1.50 (m, 12H). Anal. Calcd for $C_{17}H_{21}ClINO_5$: C, 42.39; H, 4.39; N, 2.91. Found C, 42.28; H, 4.30; N, 2.85.

**(1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl-(2*S*,4*E*)-2-(5-chloro-2-iodoanilino)-4-(2-oxo-1-phenyl-3-pyrrolidinylidene)butanoate (24).** To a solution of intermediate **22** (1.1 g, 2.3 mmol) in acetonitrile (60 mL) were added tributyl-3-(1-phenylpiperidone) phosphonium bromide **23** (1.5 g, 3.45 mmol) and DBU (0.5 mL, 3.4 mmol). The mixture was reacted at −20 °C for 3 h. 1 N HCl (50 mL) and ethyl acetate (200 mL) were added. The organic layer was separated, washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo to afford a mixture 85:15 of isomer (*E*/*Z*). Final purification by flash chromatography (cyclohexane/ethyl acetate 85:15) afforded the title compound **24** (1.05 g, 70%) as a white solid. Mp 36−39 °C; $[\alpha]^{20}_D$ +22° (*c* = 0.16, DMSO). IR (Nujol): 1741, 1694, 1660 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.75 (m, 2H), 7.63 (d, $J$ = 8.9 Hz, 1H), 7.37 (m, 2H), 7.14 (m, 1H), 6.74 (d, $J$ = 2.7 Hz, 1H), 6.52 (dd, $J$ = 8.9 Hz, 2.7 Hz, 1H), 6.41 (m, 1H), 4.97 (m, 2H), 4.72 (m, 1H), 3.84 (m, 2H), 2.80 (m, 2H), 2.66 (m, 2H), 1.40 (m, 12H). Anal. Calcd for $C_{27}H_{30}ClIN_2O_5$: C, 51.90; H, 4.84; N, 4.48. Found: C, 51.95; H, 4.90; N, 4.42.

**(1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl-(2*R*,4*E*)-7-chloro-4-(2-oxo-1-phenyl-3-pyrrolidinylidene)-1,2,3,4-tetrahydro-2-quinolinecarboxylate (25).** To a solution of intermediate **24** (0.5 g, 0.84 mmol) in toluene (100 mL) were added $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol) and triethylamine (0.16 mL, 1.17 mmol), and the mixture was heated to 110 °C for 3.5 h under an argon atmosphere. At the end of the reaction ethyl acetate (300 mL) was added. The organic phase was washed with $NH_4Cl$ (100 mL) and then brine, dried over $Na_2SO_4$, and evaporated in vacuo. Purification of the crude residue by flash chromatography (cyclohexane/dichloromethane/ethyl acetate 6.5/3/0.5) gave the title compound **25** (0.296 g, 85%) as a yellow foam. $[\alpha]^{20}_D$ −194.4 (*c* 0.692, $CHCl_3$). IR (Nujol): 3370, 1743, 1684 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.73 (m, 2H), 7.36 (m, 2H), 7.21 (d, $J$ = 8.5 Hz, 1H), 7.11 (m, 1H), 6. 98 (bm, NH), 6.75 (d, $J$ = 2.5 Hz, 1H), 6.57 (dd, $J$ = 8.5 Hz, 2.5 Hz, 1H), 4.70 (q, $J$ = 7.4 Hz, 1H), 4.24 (m, 2H), 3.75 (m, 1H), 3.18 (m, 1H), 2.05 (m, 1H), 2.94 (m, 1H), 1.25 (s, 9H), 1.23 (d, $J$ = 7.4 Hz, 3H). Anal. Calcd for $C_{27}H_{29}ClN_2O_5$: C, 67.23; H, 5.64; N, 6.82. Found: C, 67.00; H, 5.45; N, 6.72.

**(1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl (2*R*,4*S*)-7-chloro-4-(2-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1,2,3,4-tetrahydro-2-quinolinecarboxylate (26).** To a solution of intermediate **24** (0.5 g, 0.84 mmol) in DMF (20 mL) were added $Pd(OAc)_2$ (0.05 g, 0.25 mmol) and triethylamine (0.16 mL, 1.17 mmol), and the reaction mixture was stirred at 120 °C for 3 h under argon atmosphere. At the end of the reaction the solution was taken up with ethyl acetate (100 mL) and washed with $NH_4Cl$ (100 mL) and then with brine, dried over $Na_2SO_4$, and evaporated in vacuo. The final purification of the crude residue by flash chromatography (cyclohexane/dichloromethane/ethyl acetate 7:2.5:0.5) afforded compound **26 (**0.24 g, 70%) as a white foam. $[\alpha]^{20}_D$ −48.8 (*c* 0.19, $CHCl_3$). IR (Nujol): 3380, 1741, 1681 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.80 (m, 2H), 7.39 (m, 2H), 7.12 (m, 1H), 6.82 (d, $J$ = 8.5 Hz, 1H), 6.77 (d, $J$ = 2.5 Hz, 1H), 6.70 (m, 1H), 6.49 (dd, $J$ = 8.5 Hz, 2.5 Hz, 1H), 6.46 (bm, NH), 4.93 (q, $J$ = 7.2 Hz, 1H), 4.49 (m, 2H), 4.02 (m, 1H), 3.87 (m, 1H), 2.44 (m, 1H), 2.00 (m, 1H), 1.39 (s, 9H), 1.38 (d, $J$ = 7.2 Hz, 3H). Anal. Calcd for $C_{27}H_{29}ClN_2O_5$: C, 67.23; H, 5.64; N, 6.82. Found: C, 67.35; H, 5.75; N, 6.70.

**Sodium (2*R*,4*E*)-7-Chloro-4-(2-oxo-1-phenyl-3-pyrrolidinylidene)-1,2,3,4-tetrahydro-2-quinolinecarboxylate (1).** To a solution of intermediate **25** (0.29 g, 0.72 mmol) in THF/$H_2O$ (3:1) (14 mL) was added LiOH (0.069 g, 2.88 mmol), and the reaction was stirred at room temperature for 1 h. At the end of the reaction the THF was evaporated in vacuo. $H_2O$ (50 mL) was added and 3 N HCl was added dropwise until an extensive precipitation occurred (pH 3). The solid was filtered, washed with water (2 × 10 mL), and dried in vacuo at 60 °C for 12 h. The solid was dissolved in a 5% solution of methanol in ethanol (20 mL), and a 1 N NaOH solution (0.8 mL, 0.8 mmol) was added. At the end of the reaction, diethyl ether (10 mL) to the resulting suspension was added, and the solid was filtered, washed with diethyl ether (10 mL), and dried in vacuo at 40 °C for 12 h, to give compound **1** (0.24 g, 90%) as a yellow solid. Mp >200 °C; $[\alpha]_D$ −603.7° (*c* 0.316, DMSO); IR (Nujol): 1670, 1596 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.79 (m, 2H), 7.42 (m, 2H), 7.17 (d, $J$ = 8.5 Hz, 1H), 7.16 (m, 1H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.43 (dd, $J$ = 8.5 Hz, 2.5 Hz, 1H), 6.17 (bm, 1H), 4.53 (m, 1H), 3.83 (m, 2H), 3.40 (m, 1H), 3.28 (m, 1H), 2.93 (m, 1H), 2.06 (m, 1H); $^{13}C$ NMR (DMSO-$d_6$) ppm 173.34, 168.74, 148.61, 141.82, 140.91, 134.73, 129.99, 134.73, 129.99, 129.34, 124.44, 123.37, 119.81, 117.94, 113.82, 113.65, 55.61, 45.69, 27.98, 27.09. Anal. Calcd for $C_{20}H_{16}ClN_2NaO_3$: C, 61.47; H, 4.13; N, 7.17; Na, 5.88. Found: C, 61.35; H, 3.95; N, 6.99; Na, 5.95.

**Crystal Structure Analysis of the Meglumine Salt of Compound 1.** A suitable crystal was grown by slow evaporation of a DMF solution. Crystal data: $C_{20}H_{17}ClN_2O_3 \cdot C_7H_{17}NO_5$, $M$ = 564.02, monoclinic, $P2_1$ yellow crystals, $a$ = 5.7595(3) Å, $b$ = 14.2904(8) Å, $c$ = 16.2413(9) Å, $\alpha$ = 90°, $\beta$ = 94.823(2)°, $\gamma$ = 90°, 160 K, $Z$ = 2, Final $R$ indices [$F^2 > 2\sigma$] = 0.0343, GOF = 1.074. Data were collected on a Bruker SMART 1K CCD diffractometer using $\dot{\omega}$ rotation with narrow frames. The structure was solved using direct methods. Full-matrix least-squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined isotropically in riding mode. Full details can be found in the Supporting Information.

**Sodium (2*R*,4*S*)-7-Chloro-4-(2-oxo-1-phenyl-2,5-dihydro-1H-pyrrol-3-yl)-1,2,3,4-tetrahydro-2-quinolinecarboxylate (2).** To a solution of intermediate **26** (0.24 g, 0.59 mmol) in THF/$H_2O$ (3:1) (10 mL) was added LiOH (0.060 g, 2.50 mmol), and the reaction was stirred for 1 h at room temperature. The organic solvent was evaporated in vacuo, and $H_2O$ (50 mL) was added. HCl (3 N) was added until extensive precipitation occurred (pH 3). The solid was filtered, washed with water (2 × 10 mL), and dried in vacuo at 60 °C for 12 h. The solid was then dissolved in a 5% solution of methanol in ethanol (15 mL), and a 1 N solution of NaOH (0.7 mL) was added. Diethyl ether (10 mL) was added to the resulting suspension. The solid was filtered, washed with diethyl ether (10 mL), and dried in vacuo at 40 °C for 12 h to give the title sodium salt (0.186 g, 85%) as a white solid. Mp > 200 °C; $[\alpha]^{20}_D$ −102.3° (*c* 0.09, DMSO) IR (Nujol): 3383, 1669, 1598 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.79 (m, 2H), 7.37 (m, 2H), 7.10 (m, 1H), 6.80 (d, $J$ = 8.5 Hz, 1H), 6.72 (d, $J$ = 2.5 Hz, 1H), 6.36 (m, 1H), 6.34 (dd, $J$ = 8.5 Hz, 2.5 Hz, 1H), 5.71

(bm, 1H), 4.53−4.35 (m, 2H), 3.76 (m, 1H), 3.13 (m, 1H), 2.26 (m, 1H), 1.43 (m, 1H). Anal. Calcd for $C_{20}H_{16}ClN_2NaO_3$: C, 61.47; H, 4.13; N, 7.17; Na, 5.88. Found: C, 61.39; H, 4.01; N, 7.01; Na, 5.92.

***tert*-Butyl-(2*R*)-2-({(2*E*)-2-[(4-methoxyphenyl)imino]-ethanoyl}oxy)propanoate (16).** A solution of 4-methoxyaniline (0.47 g, 3.8 mmol) dissolved in toluene (5 mL) was added to the glyoxylate ester **13** (1 g, 4.5 mmol), and the solution was refluxed for 30 min in the presence of a Dean−Stark apparatus. The solvent was evaporated in vacuo obtaining aldimine **16**, as a brown oil, in quantitative yield, which was used as such in the next reaction without purification. IR (film) 1744, 1721, 1623, 1589 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 8.01 (s, 1H), 7.39 (d, 2H), 6.95 (d, 2H), 5.20 (q, $J$ = 6.80 Hz, 1H), 3.85 (s, 3H), 1.60 (d, $J$ = 6.80 Hz, 3H), 1.50 (s, 9H). $^{13}C$ NMR ($CDCl_3$) ppm 169.13, 162.70, 160.62 141.34,147.10, 124.05, 114.02, 81.80, 70.01, 55.03, 27.03, 16.30. MS (FAB) $m/z$ = 308 $[MH]^+$, 252 $[MH - t\text{-}Bu + H]^+$, 180. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56; O, 26.03. Found C, 62.78; H, 6.96; N 4.43; O 26.09.

General Procedure for the Allylmetalation Reaction (Lewis acids): (1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl-2-(4-methoxyanilino)-4-pentenoate (17a,b). To the aldimine 16 (0.37 g, 1.2 mmol) dissolved in dry $CH_2Cl_2$ (4 mL) was slowly added the Lewis acid (1.3 mmol) at −78 °C under a nitrogen atmosphere. After 20 min, allyltributyltin (0.45 mL, 1.4 mmol) was added. The reaction mixture was stirred for an additional 30 min, and then a saturated solution of $NH_4Cl$ (5 mL) and ethyl acetate (16 mL) was added. The organic phase was separated and washed with brine and dried over $Na_2SO_4$, and the solvent was evaporated in vacuo. The crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 8:2) to give a mixture of the two diastereoisomers.

**General Procedure for the Allylmetalation Reaction (Brönsted acids). (1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl-2-(4-methoxyanilino)-4-pentenoate (17a,b).** To the aldimine **16** (0.37 g, 1.2 mmol) dissolved in dry $CH_2Cl_2$ (4 mL) was slowly added the Brönsted acid (1.3 mmol) at −78 °C under a nitrogen atmosphere. After 20 min, allyltributyltin (0.45 mL, 1.4 mmol) was added. The reaction mixture was stirred for an additional 30 min, and then a saturated solution of $NH_4Cl$ (5 mL) and ethyl acetate (16 mL) was added. The organic phase was separated and washed with brine and dried over $Na_2SO_4$, and the solvent was evaporated in vacuo. The crude residue was purified by silica flash chromatography (cyclohexane/ethyl acetate 8:2) to give a mixture of the two diastereoisomers.

**17a:** $[\alpha]^{20}_D$ 91.8 (*c* 0.69, $CHCl_3$). IR ($CHCl_3$) 1739, 1510 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 6.77 (m, 2H), 6.60 (m, 2H), 5.88 (m, 1H), 5.22−5.18 (m, 2H), 4.99 (q, $J$ = 6.82 Hz, 1H), 4.12 (m, 1H), 3.88 (m, 1H), 3.74 (s, 3H), 2.71 (m, 1H), 2.63 (m, 1H), 1.47 (d, $J$ = 6.82 Hz, 3H), 1.46 (s, 9H). MS (FAB) $m/z$ = 349, 294 $[MH - t\text{-}Bu + H]^+$, 252, 176.: Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.32; H, 7.79; N, 4.01; O, 22.89. Found C, 65.51; H, 7.82; N 4.03; O 22.98.

**17b:** $[\alpha]^{20}_D$ −14.8 (*c* 0.0.65, $CHCl_3$). IR ($CHCl_3$) 1739, 151 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 6.78 (m, 2H), 6.61 (m, 2H), 5.86 (m, 1H), 5.22−5.18 (m, 2H), 4.99 (q, $J$ = 6.52 Hz, 1H), 4.13 (bm, 1H), 3.88 (bm, 1H), 3.74 (s, 3H), 2.64 (m, 2H), 1.44 (s, 9H), 1.41 (d, $J$ = 6.52 Hz, 3H).). MS (FAB) $m/z$ = 349, 294 $[MH - t\text{-}Bu + H]^+$, 252, 176. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.32; H, 7.79; N, 4.01; O, 22.89. Found C, 65.66; H, 7.90; N 4.10; O 22.90.

**(1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl-2-(4-methoxyanilino)-4-pentenoate (17a).** To allyltributyltin (1.6 g, 4.86 mmol) dissolved in dichloromethane (50 mL) was added dropwise at −78 °C $SnCl_4$ (1 M solution in toluene, 4.9 mL, 4.9 mmol). The solution was stirred for 20 min, and then intermediate **16** (1 g, 3.24 mmol), dissolved in dry dichloromethane (25 mL) was added. The reaction was stirred at −78 °C for 15 min, then a saturated solution of $NH_4Cl$ (50 mL) was added, and the resulting mixture was extracted with ethyl acetate (2 × 100 mL). The organic layers were collected and washed with a 10% solution of KF in water. The organic phase was diluted with diethyl ether (50 mL), filtered, dried over $Na_2SO_4$, and evaporated in vacuo. Final purification of the crude residue by flash chromatography (cyclohexane/ethyl acetate 95:5) gave the title compound **17a** as colorless oil.

**(1*R*)-2-*tert*-Butoxy-1-methyl-2-oxoethyl-(2*S*)-2-(4-methoxyanilino) pentanoate (18).** To a solution of **17a** (0.25 g, 0.72 mmol) in ethanol (10 mL) was added Pd/C 10% (0.18 g), and the mixture was hydrogenated in a Parr apparatus at 4 atm for 6 h. At the end of the reaction the catalyst was filtered and the solvent was evaporated in vacuo: 0.23 g (92%) of **18**, as white wax, was obtained after flash chromatography (cyclohexane/ethyl acetate 8:2). $[\alpha]^{20}_D$ 88.1 (*c* 1.24, $CHCl_3$) IR ($CHCl_3$) 1739, 1511 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 6.76 (m, 2H), 6.61 (m, 2H), 4.96 (q, $J$ = 6.50 Hz, 1H), 4.04 (m, 1H), 3.74 (s, 3H), 1.92 (m, 1H), 1.78 (m, 1H), 1.57 (m, 2H), 1.46 (d, $J$ = 6.50 Hz, 3H), 1.45 (s, 9H), 0.99 (t, 3H). MS (ES) $m/z$ = 352 $[MH]^+$, 296 $[MH - tBu + H]^+$, 178, 123. Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99; O, 22.76. Found C, 65.01; H, 8.21; N 4.03; O 22.80.

**(2*S*)-2-(4-Methoxyanilino)pentanoic acid (19).** A solution of **18** (0.23 g, 0.65 mmol) in a 2:1 mixture of THF/$H_2O$ (15 mL) and LiOH·$H_2O$ (0.11 g, 2.62 mmol) was stirred at room temperature for 4 h. After evaporation of the THF in vacuo, $H_2O$ (5 mL) and diethyl ether (30 mL) was added. After separation, the aqueous phase was acidified with HCl 5% to pH 3; the white solid precipitate was filtered and dried in vacuo to give the title compound **19** (0.1 g, 66%). $[\alpha]^{20}_D$ 71.0 (*c* 1.18, DMSO). mp = 180 °C. $^1H$ NMR (DMSO) $\delta$ 6.70 (m, 2H), 6.52 (m, 2H), 3.75 (m, 1H), 3.62 (s, 3H), 1.66 (m, 2H), 1.40 (m, 2H), 0.89 (t, 3H). MS (ES) $m/z$ = 222 $[MH]^+$, 175 $[M - COOH]^+$. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27; O, 21.5. Found C, 65.23; H, 7.55; N 6.32; O 21.4.

**Methyl-(2*S*)-2-(4-methoxyanilino)pentanoate (20).** A solution of trimethylsilyl diazomethane (2 M in hexane, 0.4 mL, 0.80 mmol) was added, at room temperature under a nitrogen atmosphere, to compound **19** (0.08 g, 0.31 mmol) dissolved in a 1:1 mixture of $CH_2Cl_2$/$CH_3OH$ (6 mL). After 2 h the solvent was evaporated in vacuo, and the crude residue was purified by flash chromatography (cyclohexane/ethyl acetate 8:2) to give the title compound **20** (0.067 g, 90%) as a yellow oil. $[\alpha]^{20}_D$ 60.1 (*c* 1.03, $CHCl_3$) IR (Nujol) 3363, 1723 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 6.77 (m, 2H), 6.60 (m, 2H), 4.00 (m, 1H), 3.83 (broad m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 1.83−1.70 (m, 2H), 1.46 (m, 2H), 0.97 (t, 3H). MS (ES) $m/z$ = 238 $[MH]^+$, 178. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90; O, 20.23. Found C, 65.73; H 7.17; N 5.82; O 20.30.

**Methyl (2*S*)-2-Aminopentanoate (21).** To a solution of intermediate **20** (0.064 g, 0.27 mmol) dissolved in acetonitrile (7.5 mL) was added, at −25 °C under a nitrogen atmosphere, ammonium cerium nitrate (0.48 g, 0.88 mmol) dissolved in $H_2O$ (0.8 mL). The reaction mixture was stirred for 40 min, and then the solvent was removed in vacuo. The aqueous solution diluted with $H_2O$ (1.5 mL) was washed with diethyl ether (2 × 5 mL), and then NaOH 0.5 M was added dropwise to pH 8 and extracted with $CH_2Cl_2$ (3 × 5 mL). The organic layers were collected, and the solvent was evaporated in vacuo. Finally, the crude residue was purified by flash chromatography (100% ethyl acetate) to give title compound **21** (0.016 g, 45%) as a pale yellow oil. $[\alpha]^{20}_D$ −15.3 (*c* 0.57, DMSO). IR ($CHCl_3$) 2961, 1733 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 3.74 (s, 3H), 3.47 (m, 1H), 1.71 (m, 2H), 1.55 (m, 2H), 1.42 (m, 2H), 0.95 (t, 3H). MS (ES) $m/z$ = 132 $[MH]^+$. Anal. Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68; O, 24.39. Found C, 55.01; H 9.86; N 10.70; O 24.48.

**Supporting Information Available:** $^1H$ NMR spectra for compounds **1**, **2**, **17a**, **17b**, **15a**, **22**, **24**, **25**. X-ray crystallographic data for compound **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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